41. (Amended) The method of claim 40 wherein said screening step further comprises reacting one or more volatile organic tags with the medium to attach to said nucleic acid.

42. (Twice amended) A method according to claim 1, wherein the enzymatic biomolecular reaction is a polymerase chain reaction.

44. (Amended) A method according to claim 42 wherein said reaction is a Taq-mediated PCR.

REMARKS

Claims 1, 4-18, 25-26, 36-37 and 40-44 are pending. The Applicant herein respectfully requests further examination of the application and reconsideration of the claims, in view of the amendments[1] and remarks presented herein.

I. The Examiner has rejected claims 1-4, 6, 8, 10-18, 25-26, 35 and 36-43 under 35 USC §103(a) as obvious over Nova '026, in view of Payne '701 and Harris WO'634. Claim 44 is rejected further in view of Takakura '185.

The Applicant respectfully reminds the Examiner that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be a material suggestion or motivation to modify the reference or to combine reference teachings. Second, **there must be a reasonable expectation of success that the combination will succeed; and finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations**. The teaching to make the claimed combination *and* the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The Applicant will outline, as follows, how one of ordinary skill in the art would not be motivated to combine and employ the elements of the invention now claimed. *Moreover*, even if the elements were combined as suggested by the

[1] Attached hereto, for the convenience of the Examiner, is a marked version of the claims now pending to show amendments presented herein.

Examiner, the proposed modification would render the prior art invention (Nova '026) being modified unsatisfactory for its intended purpose.

NOVA '026

The Applicant respectfully points out that the disclosure of Nova '026 is drawn toward the use of known *substrate-bound* molecules - in combination with a memory device - "matrix with memories" - to specifically detect molecular interactions, i.e., the physical binding between the support-bound molecules *on the matrix* and molecules in the system. Specifically, the Nova device is for attaching molecules of interest to a support substrate (matrix)[2] and detecting, by means of a memory device linked to the support substrate, subsequent intra-system interactions between the support-bound molecules and systemic reagents.[3] Applications of the Nova "matrix with memories" are *specifically limited* to those which specifically require molecular interactions, i.e., physical binding, between the support-bound molecules on the matrix and molecules in the system. Nova '026 requires the attachment of known compounds to a matrix (or mixtures of known compounds in multianalyte analyses) whereby unknown compound(s) are identified by detection of a physical interaction with the known compound(s) (i.e., to label or track unknown entities and thereby identify the unknown by virtue of a reaction with the known compound). The Nova substrate device is limited to binding assays and solid-state synthesis applications, e.g., immunoassays, drug screening assays, combinatorial syntheses, and affinity separation procedures that specifically require physical binding between the support-bound molecules and molecules in the system.

The Applicant respectfully points out to the Examiner that the subject matter of the present invention, in sharp contrast to the binding method of Nova, is a method of sampling

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[2] "As used herein, a matrix refers to any solid or semisolid or insoluble support on which a code is to which the memory device and/or the molecule of interest, typically a biological molecule, organic molecule or biospecific ligand is linked or contacted." Nova, Spec. Col.18, lines 17-21, *et seq.* "Thus, as used herein, matrix refers to materials that have been so-treated." Nova, Spec. Col.19, lines 1-2.

[3] It is, moreover, unambiguously emphasized in the Nova'026 disclosure that the support-bound molecules linked to memory are not sensors. "It is, however, emphasized that the combinations herein of matrix with memory are not sensors, which measure external parameters ... the linked or associated biological particle or matrix is written into the memory, and thus records information about itself. Sensors [in contrast] monitor what is going outside of the device. Nova, Spec. Col.31, lines 24-32.

volatile compounds within a gas phase of a nucleic acid reaction, e.g., an accumulation cycle of nucleic acids,[4] by detecting physico-chemical[5] changes of a nucleic acid by means of a multisensor array, including gas sensors, for example, solid-state semiconductor sensors, metal oxide electrodes, optical fibers, and/or mass spectrometers. *See*, e.g., para. 29, 59, 64, and 69 with reference to the instant published application 20020094531, *or*, with reference to the document, as filed, p.13, lines 6-15; p.21, line 24-p.22, line 16; p.23, line 23-p.24, line 3; and p.25, lines 8-10, respectively.

Since Nova '026 teaches a method for monitoring *binding* information on a *solid* medium, i.e., binding on a matrix (substrate); Nova alone, as a matter of law, cannot render the subject matter of any of the instant claims obvious since all claims to the instant invention require monitoring an enzymatic biomolecular reaction, by means of monitoring *volatile compounds in a gas or vapor phase* medium. The Examiner, however, has rejected the Applicant's claims as obvious over Nova '026, in view of Payne '701 and Harris WO'634.

It is axiomatic that a claimed invention is not obvious solely because it is composed of elements that are all individually found in the prior art. *See, e.g.*, In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1044, 1051, 5 USPQ 1434, 1438 (Fed. Cir. 1988). **The need for specificity pervades this authority**. *See, e.g.*, In re Kotzab, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).[6]

The Examiner has alleged that although Nova does not teach embodiments wherein the "matrix" (substrate) is a gas sensor, Payne teaches a gas sensor - and that it would be *prima facie*

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[4] As stated in paragraphs 35 (page 15, lines 19-21) and 65 (page 24, lines 4-6) of the specification, the written description of the invention refers to nucleic acids.

[5] Including photophysical and chemical properties. *See*, e.g., instant spec. para.34 (p.15, lines 1-4).

[6] "The factual inquiry whether to combine references must be thorough and searching." McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). This precedent has been reinforced in myriad decisions, and cannot be dispensed with. See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000).

obvious to one of ordinary skill at the time of the invention to employ the gas sensor of Payne in the method of Nova.

Payne, *et al.*, '701, describes a method for identifying a microorganism that includes abstracting gas or vapor associated with the microorganism and flowing it over a gas sensor observing the response of the sensor.[7] Applications of the Nova "matrix with memories", however, are specifically limited to those which specifically require molecular interactions, i.e., physical binding, between the support-bound molecules on the matrix and molecules in the system (binding assays and/or chemical synthesis). Nova particularly requires *binding* of compounds to the matrix either for assays or synthesis applications and literally distinguishes "sensors". Nova, Spec. Col.31, lines 24-25. Accordingly, gas sensors, *per se*, are not relevant to the Nova disclosure or any applications described therein and are in fact categorically excluded from the scope of the disclosure. **If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification**. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP §2143.01. Accordingly, the Applicant respectfully points out that, categorically excluded from the '026 description, a gas sensor would render the Nova method unsatisfactory for its intended purpose, i.e., physically detecting *binding interactions that occur on the substrate* ("matrix") *itself*.

Consequently, one of ordinary skill in the art would not be motivated to modify the matrix (substrate) of Nova to a gas sensor of Payne, or *vice versa*.

Harris WO'634 teaches a solid-phase diagnostic method for detecting a specific target nucleic acid sequence which involves PCR amplification of the target nucleic sequence and a solid-phase hybridization oligomer for detection. Harris relates to detection of target nucleic acids by conventional means, i.e., hybridization, - the only alleged novelty aspect being that the capture oligomer is immobilized. Harris WO'634, however, is not material or relevant in any way to the instant method for monitoring the state or progress an enzymatic biomolecular reaction, by means of monitoring volatile compounds in a gas or vapor phase medium.

The Applicant respectfully submits that claim 44 merely limits the subject matter of the invention to the use of a polymerase *reagent* derived from a particular bacterial species, i.e.,

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[7] Payne does not contemplate monitoring a nucleic acid reaction.

Thermus aquaticus (Taq). Accordingly, Takakura is not material to the substance or material elements of the claimed invention. The legal determination under section 103 is whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

The Applicant accordingly respectfully requests that the Examiner withdraw the obviousness rejections under 35 USC §103(a) over Nova '026, in view of Payne '701 and Harris WO'634 and further in view of Takakura '185.

II. The Examiner has rejected claims 1-4, 6-18, 19, 21, 25-26, 35 and 36-41 under 35 USC §103(a) as obvious over Nova '026, in view of Payne '701 and further in view of Harris WO'634 and Ashe '270.

The disclosure of Ashe '270 relates to a method for preparing lubricating oils by predicting performance, perceptual, chemical or physical properties of streams entering or exiting units in the lubes manufacturing process using a combination of gas chromatography and mass spectrometry. The Examiner alleges, *inter alia*, that since mass spectrometers were basically known in the art at the time of the invention, e.g., Ashe teaches a micromechanical mass spectrometer, it would have been *prima facie* obvious to one of ordinary skill to combine the mass spectrometer as employed by Ashe with the disclosures of Nova, Payne, and Harris to reach the Applicant's claimed invention.

The Applicant respectfully points out that the combination of Nova, Payne, Harris, and Ashe necessarily fails as a matter of law to render obvious the subject matter of the claims presented herewith obvious because, as emphasized *supra*, the legal determination under section 103 is whether the claimed invention *as a whole* would have been obvious to a person of ordinary skill in the art at the time the invention was made. The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion

or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP §2143.01. Accordingly, the Applicant respectfully submits that a mass spectrometer would render the Nova method unsatisfactory for its intended purpose, i.e., physically detecting *binding* interactions.

The Applicant accordingly respectfully requests that the Examiner withdraw the obviousness rejection under 35 USC §103(a) over Nova '026, in view of Payne '701 and Harris WO'634 and further in view of Ashe '270.

III. The Examiner has rejected claims 1-6, 8, 10-18, 25-26, and 36-41 under USC §103(a) as obvious over Nova '026, in view of Payne '701 and further in view of Harris WO'634 and Ghahramani '373.

The disclosure of Ghahramani '373 relates to a highly visible, easily deployed multiple hazard marker and multiple hazard marker system for breach lanes through a minefield, biohazard warning, chemical warning, buried power and fluid transmission lines, construction zones, surveying sites, flood warning, fire zone warnings, and blasting zones. The Examiner alleges that since Ghahramani teaches a metal oxide gas sensor, it would have been *prima facie* obvious to one of ordinary skill to combine the metal oxide gas sensor as employed by Ghahramani with the disclosures of Nova, Payne, and Harris to reach the Applicant's claimed invention.

The Applicant respectfully points out that the combination of Nova, Payne, Harris, and Ghahramani necessarily fails as a matter of law to render obvious the subject matter of the claims presented herewith obvious because, as presented *supra*, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Furthermore, the Applicant points out that a metal oxide gas sensor is categorically excluded from the '026 description and moreover would render the Nova method unsatisfactory for its intended purpose.

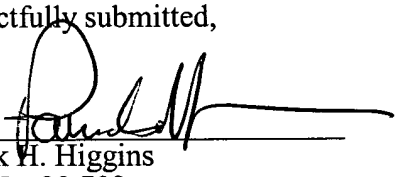
The Applicant accordingly respectfully requests that the Examiner withdraw the obviousness rejection under 35 USC §103(a) over Nova '026, in view of Payne '701 and Harris WO'634 and further in view of Ghahramani '373.

* * *

For all the foregoing reasons, the Applicant submits that Claims 1, 4-18, 25-26, 36-37 and 40-44 are in condition for allowance. Early action toward this end is courteously solicited. *The Examiner is kindly encouraged to telephone the undersigned in order to expedite any detail of the prosecution*.

A check in the amount of $465.00 to cover the cost of the three-month extension is enclosed. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2165.

Respectfully submitted,



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Marked Copy of Pending Claims

1. (Thrice Amended) A method for monitoring an enzymatic [mediated] biomolecular reaction which reaction is performed in a medium comprising at least one biomolecule [, the method], by means of monitoring volatile compounds in a gas or vapor phase medium, wherein said medium is a mixture of one or more enzymatic nucleic acid reagents or products, comprising the steps of:

screening the medium with a screening means comprising a [n number of sensing probes, where n is an integer of at least one] multisensor array so that more than one [physical, chemical, or] physico-chemical change of a gas or vapor phase of a nucleic acid can be [at least one secondary product of the biomolecule, a biomolecule byproduct or the biomolecule which defines the information is] detected by the multisensor, thereby providing information [probe] to produce at least one signal output [, said medium is a mixture of one or more of enzymatic products, amplicon byproducts, primer byproducts, cloned products, polymerase chain (PCR) products, secondary products, PCR byproducts or reagents and said biomolecule is at least one of DNA, RNA or a nucleotide];

transferring the signal output to a signal processing means responsive to differences in electromagnetic properties of the signal for generating a final output;

receiving the final output into a pattern recognition means sufficient to generate a measurement pattern of the information;

sorting the information in accordance with a set of class boundaries of [physical, chemical or] the physico-chemical changes [of the biomolecule representative of the presence and quantitative amounts of the biomolecule in the medium]; and

monitoring [the] sorted information [for monitoring said enzymatic mediated biomolecular reaction] representative of the identity and amount of a nucleic acid in the medium.

4. (Amended) The method according to claim 1, wherein the multisensor array comprises [sensing probe is] a semiconductor gas sensor.

5. (Amended) The method according to claim 1, [wherein the medium is a gas or a vapor, and] wherein the multisensor array [sensing probe] comprises at least one of a doped metal oxide gas sensor or an undoped metal oxide gas sensor [used in gas or vapor phase].

6. (Amended) The method according to claim 1, wherein the multisensor array [sensing probe] comprises at least one conductive polymer sensor.

7. (Amended) The method according to claim 1, wherein the multisensor array [sensing probe] is at least one of a vibrating or resonant micromechanical device.

8. (Amended) The method according to claim 7, wherein the multisensor array [sensing probe] has a coating.

9. (Amended) The method according to claim 1, wherein the multisensor array [n number of sensing probes] is a mass spectrometer.

10. (Amended) The method according to claim 1, wherein the multisensor array [sensing probe is] comprises an optical sensing probe.

11. (Amended) The method according to claim 1, wherein the multisensor array [sensing probe is, at least in part,] comprises an optical fiber.

12. (Amended) The method according to claim 1, wherein the information comprises at least one of odorous or volatile chemical species characteristics of the presence of a nucleic acid [the biomolecule or the part of the biomolecule].

13. (Amended) The method according to claim 1, wherein at least part of the information detected by the multisensor array [probe] is changes in the concentration of a nucleic acid [the biomolecule].

14. (Twice amended) The method according to claim 1, wherein at least part of the information detected by the multisensor array [probe] is changes in the at least one secondary product of the reaction [biomolecule].

15. (Amended) The method according to claim 1, wherein at least part of the information detected by the multisensor array [probe] is changes in a radiative property of the electromagnetic spectrum of a nucleic acid [the biomolecule].

16. (Amended) The method according to claim 1, wherein at least part of the information detected by the multisensor array [probe] is changes in a non-radiative property of the electromagnetic spectrum of a nucleic acid [the biomolecule].

17. (Amended) The method according to claim 1, wherein at least part of the information detected by the multisensor array [probe] is changes in a non-radiative property of the electromagnetic spectrum of a secondary product of the reaction [biomolecule].

18. The method according to claim 1, wherein the medium comprises at least one of organic or inorganic reagent.

25. The method according to claim 10, wherein the optical sensing probe is an apertured probe.

26. The method according the claim 10, wherein the optical probe is an apertureless probe.

36. The method of claim 1, further comprising the step of comparing the class boundaries with properties of a second group of signal outputs.

37. (Amended) The method of claim 1 wherein said screening step further comprises reacting one or more volatile organic tags with the medium to attach to said nucleic acid [biomolecule].

40. The method of claim 1 further comprising the step of:

controlling a polymerase chain reaction after the step of monitoring the sorted information.

41. (Amended) The method of claim 40 wherein said screening step further comprises reacting one or more volatile organic tags with the medium to attach to said nucleic acid [biomolecule].

42. (Twice amended) A method according to claim 1, wherein the enzymatic [mediated] biomolecular reaction is a polymerase chain reaction [PCR].

44. (Amended) A method according to claim 42 [43] wherein said reaction [polymerase] is a Taq-mediated PCR.

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